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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,086	10/08/2003	Hans-Peter Hohmann	20606 US (C038435/0111674	7182

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,086	HOHMANN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-32 are pending.

Applicants' amendment filed July 20, 2006 is acknowledged. Applicants' response has been fully considered. Claims 23 and 24 have been amended. Claims 23-32 are examined.

Oath/Declaration

2. A new oath or declaration filed July 20, 2006 is acknowledged.

Withdrawn Objection to Abstract

3. A new abstract on a separate sheet filed July 20, 2006 is acknowledged.

Withdrawn Claim Rejections -Obviousness Type Double Patenting

4. The previous rejection of claim 32, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U. S. Patent 6,656,721, is withdrawn in view of applicants' response at pages 15-16 in the amendment filed July 20, 2006.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a process for decoupling production of a specific target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism of bacillus that contains a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product (i.e., riboflavin), and (b) introducing a biotin auxotrophy into the microorganism to control biomass

production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a microorganism made by the process, wherein the microorganism is a riboflavin production bacillus microorganism and transformed with the polynucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for a process for decoupling production of a target fermentation product from biomass production in a fermentation medium comprising: (a) providing a recombinantly produced microorganism of bacillus that contains a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product, and (b) introducing a biotin auxotrophy into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a microorganism made by the process, where the structures of recombinantly produced microorganism of bacillus and biotin auxotrophy-causing polynucleotides are not identified, and the target fermentation product is pantothenic acid, thiamin, folic acid or pyridoxine. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23-32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of bacillus and introducing a biotin auxotrophy into the microorganism; and a microorganism made by the process, wherein the target fermentation product is riboflavin, pantothenic acid, thiamin, folic acid or pyridoxine. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a process for decoupling production of a target fermentation product from biomass

production in a fermentation medium. This process includes providing a recombinantly produced microorganism that has been engineered to contain a polynucleotide sequence which encodes the biosynthetic enzymes for a target fermentation product, where the maximal production of the target fermentation product is dependent on an unlimited supply of a target fermentation product substrate for the microorganism. Next, an auxotrophy is introduced into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a fermentation production microorganism made by the process. There are no indicia that the present application enables the full scope of the claims in view of the claimed method as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the recombinantly produced microorganisms of bacillus containing the polynucleotide sequences which encode biosynthetic enzymes for the target fermentation products of pantothenic acid, thiamin, folic acid or pyridoxine, and biotin auxotrophy-causing polynucleotides, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations (see Examples 1-3). However, the specification has not identified various recombinantly produced microorganisms that contain polynucleotides encoding biosynthetic enzymes for producing target fermentation products of pantothenic acid, thiamin, folic acid or pyridoxine, and various biotin auxotrophy-causing polynucleotides, and their use in the claimed method.

(3). The state of the prior art and relative skill of those in the art:

The related art (references on pages 1-4 of the specification) teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art contains many examples of required genes whose mutation is likely to cause auxotrophy (e.g., Dev et al. (1984), cited in IDS). While the art teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways, the polynulceotides encoding biosynthetic enzymes for producing target fermentation products of pantothenic acid, thiamin, folic acid or pyridoxine are not taught by the specification. Since the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on identification of various recombinantly produced microorganisms of bacillus that contain polynucleotides encoding biosynthetic enzymes for producing target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine, and various biotin

auxotrophy-causing polynucleotides, and the use of these recombinantly produced microorganisms in the claimed method.

(4). Predictability or unpredictability of the art:

The claims encompass a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of a bacillus and introducing a biotin auxotophy into the microorganism; and a microorganism made by the process. Since the polynucleotides that encode biosynthetic enzymes for producing target fermentation products of pantothenic acid, thiamin, folic acid or pyridoxine are not disclosed in the specification, and the number of possible mutations for mutated genes that cause biotin auxotrophy is virtually endless, the structures of recombinantly produced microorganisms of bacillus containing these polynucleotides are unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of a bacillus and introducing a biotin auxotophy into the microorganism; and a microorganism made by the process. The specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations (see Examples 1-3). However, the specification has not taught the polynucleotides encoding biosynthetic enzymes for producing target fermentation product of pantothenic acid, thiamin, folic acid or

pyridoxine, nor has identified various recombinantly produced microorganisms of bacillus that contain the polynucleotides encoding biosynthetic enzymes for producing the target fermentation product, and various biotin auxotrophy-causing polynucleotides, and their use in the claimed method. Moreover, there are no working examples demonstrating the use of various recombinantly produced microorganisms transformed with various biotin auxotrophy-causing polynucleotides. Since the specification does not provide sufficient teachings on identities of polynucleotides encoding biosynthetic enzymes for producing the target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine and of various biotin auxotrophy-causing polynucleotides in the recombinantly produced microorganisms of bacillus, and their use in the claimed method, it is necessary to carry out undue experimentation to identify the functional recombinantly produced microorganisms of bacillus that would produce sufficient amount of target fermentation product in the claimed method.

(6). Nature of the Invention

The scope of the claim encompasses a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of a bacillus and introducing a biotin auxotophy into the microorganism; and a microorganism made by the process, but the specification does not provide sufficient teachings on the identities of various recombinantly produced microorganisms of bacillus that contain polynucleotides encoding biosynthetic enzymes for producing target fermentation product and various biotin auxotrophy-causing polynucleotides, and their use in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method associated with variants, the teachings in the specification are limited, and the sequences of biotin auxotrophy-causing polynucleotides and the structures of functional recombinantly produced microorganisms of bacillus are unpredictable, and therefore, it is necessary to carry out undue experimentation to identify the functional variants.

Response to Arguments

Applicant indicates claim 23 has been amended to recite (1) that the recombinantly produced microorganism is a Bacillus, (2) that biotin is the specific auxotrophy, and (3) that riboflavin, pantothenic acid, thiamin, folic acid, and pyridoxine are the specific target fermentation products. With these amendments, the scope of claims 23-32, regarding "unspecified variants" are rendered moot. Furthermore, in view of the disclosure in the specification for the B. subtilis strain, a skilled person would certainly know how to manipulate other Bacilli strains in order to produce one of the claimed target fermentation products - riboflavin, pantothenic acid, thiamin, folic acid, or pyridoxine - which all belong to the vitamin B complex and are thus also closely related to each others. The genes involved in the riboflavin biological pathway are well known in the art, also the claimed target fermentation products are well known and available in the art. Thus, there would be no undue experimentation to take the information disclosed with regards to the rib genes over expressed as exemplified by B. subtilis RB50 and the guidance given in the specification regarding the introduction of biotin auxotrophy by mutating the microorganism, and arrive at applicants currently claimed invention. Moreover, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. Accordingly, ample guidance is

provided in the specification, and the rejection should be withdrawn (pages 8-12 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. While claim 23 has been amended to recite the recombinantly produced microorganism is a Bacillus, biotin is the specific auxotrophy, and riboflavin, pantothenic acid, thiamin, folic acid, and pyridoxine are the specific target fermentation products, there are still considerable variants encompassed by the claims, e.g., the polynucleotides encoding biosynthetic enzymes for producing target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine, various biotin auxotrophy-causing polynucleotides, and recombinantly produced microorganisms of bacillus that contain such polynucleotides. Although the target fermentation products are limited to riboflavin, pantothenic acid, thiamin, folic acid, and pyridoxine, and the genes involved in the riboflavin biological pathway are well known in the art, the specification does not provide sufficient teachings on the genes encoding biosynthetic enzymes for producing target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine; mutated polynucleotides that cause biotin auxotrophy; and recombinantly produced microorganisms of bacillus that contain such polynucleotide, thus, a skilled person would not know how to manipulate a Bacilli strain to produce one of the claimed target fermentation products such as pantothenic acid, thiamin, folic acid, and pyridoxine. Regarding the mutated polynucleotides that cause biotin auxotrophy, since there is only one specific sequence of SEQ ID NO:1 shown, and no structure/activity correlation on the mutated polynucleotide variants is indicated, a skilled person would not know how to choose a proper mutated polynucleotide that cause biotin auxotrophy from unlimited number of polynucleotide

variants. Without further guidance/teachings, one skilled person would not how to make/use recombinantly produced microorganisms of bacillus that contain the required polynucleotides. Therefore, it is necessary to carry out undue experimentation to identify the recombinantly produced microorganisms of bacillus that would produce sufficient amount of target fermentation product in the claimed method. Thus, the full scope of the claims are not enabled.

6. Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23-32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of bacillus and introducing a biotin auxotrophy into the microorganism; and a microorganism made by the process, wherein the target fermentation product is riboflavin, pantothenic acid, thiamin, folic acid or pyridoxine. While the specification indicates that the invention provides a process for decoupling production of a target fermentation product from biomass production in a fermentation medium by introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into *bacillus subtilis* RB50 containing multiple copies of the engineered *rib* operon pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations, which shows the product yield (i.e., the amount of riboflavin produced on the consumed glucose) is 33% higher in the decoupled process to the coupled process (see Examples 1-3), the specification does not disclose a genus of variants for

recombinantly produced microorganisms of bacillus that contain a polynucleotide sequence that encodes biosynthetic enzymes for a target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine, and biotin auxotrophy-causing polynucleotides. A single working example (culturing RB50::[pRF69]Bio$^-$ transformed with SEQ ID NO:1 at different biotin concentration to produce riboflavin; Example 3) does not provide written description for the genus of variants in the claimed method. Furthermore, the specification does not disclose polynucleotide sequences that encode biosynthetic enzymes for a target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine, various mutations in the biotin auxotrophy-causing polynucleotide sequences, and recombinantly produced microorganisms of bacillus that contain such polynucleotides. Without guidance on the polynucleotide sequences that encode biosynthetic enzymes for a target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine; various mutations in the biotin auxotrophy-causing polynucleotide sequences; and recombinantly produced microorganisms of bacillus that contain such polynucleotides, as well as structure to function/activity for biotin auxotrophy-causing polynucleotides, one skilled in the art would not know how to identify the functional variants used in the claimed method. The lack of description on the structures of recombinantly produced microorganisms of bacillus that contain polynucleotide sequences encoding biosynthetic enzymes for the target fermentation product, and biotin auxotrophy-causing polynucleotides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicant indicates claim 23 has been amended to recite (1) that the recombinantly produced microorganism is a Bacillus, (2) that biotin is the specific auxotrophy, and (3) that riboflavin, pantothenic acid, thiamin, folic acid, and pyridoxine are the specific target fermentation products. With these amendments, regarding "no alleged disclosure of a genus variants for target fermentation products, recombinantly produced microorganisms that contain a polynucleotide sequence which encodes biosynthetic enzymes for a target fermentation product, and auxotrophy-causing polynucleotides," are rendered moot. Furthermore, with Examples 1-3 the description on the microorganism of bacillus carrying an biotin auxotrophy in the specification (e.g., pages 11, 12 and 14), there is sufficient information disclosed within the specification for one of skill to easily determine whether a strain would fall within the currently amended claims. Moreover, the specification provides ample information detailing the knowledge in the art regarding the currently claimed process. (See, e.g., Specification at pages 11-18 and Examples 1-3). In view of the foregoing, the inventors were in possession of the currently claimed process at the time the application was filed (pages 12-15 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. While the target fermentation products are limited to riboflavin, pantothenic acid, thiamin, folic acid, and pyridoxine, and the genes involved in the riboflavin biological pathway are well known in the art, the specification does not provide sufficient teachings on the genes encoding biosynthetic enzymes for producing target fermentation product of pantothenic acid, thiamin, folic acid or pyridoxine; the mutated polynucleotides that cause biotin auxotrophy; and recombinantly produced microorganisms of bacillus that contain such polynucleotide, thus, a skilled person would not know how to produce

a recombinantly Bacilli strain that produces the target fermentation products such as pantothenic acid, thiamin, folic acid, and pyridoxine in the claimed method. Furthermore, there is only one specific sequence of SEQ ID NO:1 shown as the mutated polynucleotides that cause biotin auxotrophy, and no structure/activity correlation on the mutated polynucleotide variants is indicated, a skilled person would not know how to choose a proper mutated polynucleotide that causes biotin auxotrophy from unlimited number of polynucleotide variants. Without description on the structures of recombinantly produced microorganisms of bacillus that contain required polynucleotide sequences, and the lack of representative species as encompassed by the claims, one skilled person, applicants have failed to sufficiently describe the claimed invention, and a skilled artisan would not recognize applicants were in possession of the claimed invention.

Conclusion

7. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner 

primary CHIH-MIN KAM
PATENT EXAMINER

CMK
September 22, 2006